*Anti-Cancer Drugs 2000,* **11,** pp. 101–108

## Clinical report

# Interferon-α and 13-*cis*-retinoic acid as maintenance therapy after high-dose combination chemotherapy with growth factor support for small cell lung cancer—a feasibility study

**Tarja Ruotsalainen,[1] Maija Halme,[1] Olli-Pekka Isokangas,[2] Seppo Pyrhönen,[3] Matti Mäntylä,[2] Markku Pekonen,[4] Seppo Sarna,[5] Heikki Joensuu[2] and Karin Mattson[1]**

[1]Department of Internal Medicine, Division of Pulmonary Medicine and [2]Department Radiotherapy and Oncology, Helsinki University Central Hospital, 00290 Helsinki, Finland. [3]Department Radiotherapy and Oncology, Turku University Central Hospital, 20520 Turku, Finland. [4]Savonlinna Central Hospital, 57170 Savonlinna, Finland. [5]Department of Public Health, University of Helsinki, 00300 Helsinki, Finland.

**This randomized phase II multi-center study was designed to determine the time to progression, duration of response and the feasibility of an intensified maintenance regime consisting of a combination of interferon (IFN)-α and retinoic acid after high-dose combination chemotherapy and radiotherapy in patients with small cell lung cancer. The patients received four courses of combination chemotherapy consisting of ifosfamide, carboplatin and etoposide, with higher doses of ifosfamide and carboplatin given in the first course, with routine growth factor support. Responding patients were then randomly assigned to one of three maintenance therapy arms. All patients with limited disease (LD) were given thoracic radiotherapy before maintenance therapy and those who had also achieved a complete response (CR) or minimal residual disease (MRD) received prophylactic cranial irradiation. In Arm 1 patients received IFN-α-2a, 6 MIU s.c. TIW for 4 weeks, followed by 3 MIU s.c. TIW, and 13-*cis*-retinoic acid 1 mg/kg/day p.o. BID daily. In Arm 2 patients received trophosphamide 100–150 mg/day p.o. BID. No maintenance treatment was given in Arm 3, the control group. Maintenance therapy was continued for 1 year. Eighty-five patients were treated according to the protocol. Twenty-one patients achieved CR, four achieved MRD and forty-two achieved partial responses to chemotherapy and radiotherapy. Sixty patients (71%) were randomly assigned for maintenance treatment. Median survival was 17.1 months in the IFN-α–retinoic acid arm, 12.4 months in the trophosphamide arm and 13.5 months in the control arm. One-year survival rates were 82, 56 and 55%, respectively. Duration of response was 6.5, 5.5 and 4.7 months, respectively. Time to progression was 8.6, 8.0 and 6.8 months, respectively The differences were not statistically significant. The IFN-α–retinoic acid maintenance treatment was well tolerated. Patients who received IFN-α–retinoid maintenance therapy lived longer after the onset of progressive disease. The treatment regime was effective, feasible and well tolerated.** 

*Key words*: Chemotherapy, interferon-α, 13-*cis*-retinoic acid, small cell lung cancer.

## Introduction

Initial treatment with chemo- and radiotherapy, separately or in combination, produces high response rates in small cell lung cancer (SCLC), but subsequent relapse is inevitable. In untreated SCLC, median survival (MS) is approximately 3 months. In large series MS is 8 months for patients with extensive disease and 14 months for those with limited disease (LD), after combination chemotherapy.[1] There has been a trend in recent years to reduce the number of treatment cycles in the induction phase.[2] At the same time, efforts have been made to potentiate the chemotherapy by using higher doses of drugs together with growth factors[3] to prevent or delay subsequent relapse, although conventional doses may still have a clinically useful impact on response duration and survival.[4] Analysis of 21 phase III trials initiated in North America and the SEER database from 1972 to 1994 demonstrates that there has been little change in the MS of patients with extensive-stage SCLC over the

This work was supported by a grant from the Finnish Antituberculosis Association.

Correspondence to K Mattson, Department of Internal Medicine, Division of Pulmonary Medicine and Clinical Physiology, Helsinki University Central Hospital, Haartmaninkatu 4, 00290 Helsinki, Finland.
Tel: (+358) 9 4717.2270; Fax: (+358) 9 2418.717;
E-mail: karin.mattson@HUCH.fi

last 10 years. Twenty-two years of clinical research using the available chemotherapy has achieved an improvement of only 2 months in the survival of patients with extensive-stage SCLC.[5]

It is therefore of interest to investigate novel therapies using, for example, biological response modifiers to prolong remission. Interferon (IFN) was the first cytokine to be used in the biological therapy of malignant diseases in the 1970s. IFNs are glycoproteins produced by many types of cells in response to foreign proteins such as viruses, microbes or tumors. The direct effect of IFN may be antiproliferative, cytostatic or cytotoxic. The Helsinki Lung Cancer Group has performed several sequential randomized studies to find the optimal way to use IFN in the overall treatment of SCLC.[6–8] Initially, high-dose IFN-α was given as monotherapy before chemoradiotherapy to patients with previously untreated limited disease SCLC. The results suggested that natural IFN-α had some biological activity against SCLC.[6] We then investigated maintenance treatment with natural IFN-α and found that it significantly prolonged survival for patients with limited disease and improved the long-term survival of SCLC patients for whom other prognostic factors were favorable.[7,9] We have also shown that IFN can be administered concomitantly with standard (cisplatin–etoposide) chemotherapy, but that the doses of chemotherapy often had to be reduced because of hematological toxicity.[8]

We designed this randomized study to see if maintenance therapy could be improved by combining IFN-α with 13-*cis* retinoic acid. Laboratory data and clinical experiments suggest that retinoids (analogs of vitamin A or retinol) have the potential to prevent and inhibit carcinogenesis, and could be used as adjuvants in the management of early stage disease.[10] Retinoids combined with IFN-α have been shown to have synergistic effects on growth inhibition and the induction of differentiation. 13-*Cis*-retinoic acid is a vitamin A derivative belonging to the retinoid group, which has been found to inhibit cell proliferation, induce cell differentation and inhibit angiogenesis.[11] IFN-α has been found to increase the efficiency of the anti-cancer effects of retinoids in some studies, and favorable responses have already been seen in clinical trials using the combination of retinoids and IFN-α, e.g. in the treatment of squamous cell carcinoma.[12]

The induction treatment in this study consisted of four cycles of ICE (ifosfamide–carboplatin–etoposide) chemotherapy and sequential thoracic irradiation for patients with LD. Patients were then randomized to receive IFN-α+13-*cis*-retinoic acid maintenance therapy, trophosphamide maintenance or no maintenance, for 1 year. The main endpoints were time to progression, duration of response, treatment feasibility and toxicity of IFN-α+13-*cis*-retinoic acid maintenance therapy.

## Patients and methods

We enrolled patients with histologically or cytological confirmed diagnosis of SCLC. Patients with previously untreated stage I–IV SCLC, with measurable tumor (in one or two dimensions) and age between 18 and 70 years were eligible. Patients were required to have a Karnofsky index $\geqslant 60\%$, WBC $\geqslant 4.0 \times 10^9$/l, platelets $\geqslant 100 \times 10^9$/l, creatinine, creatinine clearance and bilirubin within normal reference range, cholesterol $<8$ mmol/l, and aspartate aminotransferase $<3\times$ upper limit of reference range (if liver metastases were present $<5\times$ upper limit of reference range). Written informed consent was required.

Exclusion criteria were pregnancy and breast feeding (women of child-bearing age were expected to use efficient contraception during the study), other serious disease than SCLC (recent cerebral or myocardial infarction, $\leqslant 3$ months), simultaneous treatment with other investigational cancer drugs, expected survival $\leqslant 3$ months, inability to comply with drug therapy, hyperlipidemia and A vitaminosis.

The patients received four courses of combination chemotherapy consisting of a first course of high doses with growth factor support, and three courses using standard doses of ifosfamide, carboplatin and etoposide at 3 week intervals. The original protocol included epirubicin (90 mg/m$^2$ in the first course and 70 mg/m$^2$ in the other courses) but this was removed after the first four patients had been treated, because of toxicity. The first course of elevated doses with routine growth factor (granulocyte colony stimulating factor) support comprised ifosfamide (Holoxan®; Asta Medica, Tampere, Finland) 5 g/m$^2$ i.v. day 1, 3–4 h infusion+mesna (Uromitexan®; Asta Medica) 50%, 25%, 25%, carboplatin (Paraplatin®; Bristol Myers Squibb, Espoo, Finland) 300 mg/m$^2$ i.v. day 1, etoposide (Vepesid®; Bristol Myers Squibb) 120 mg/m$^2$ i.v. days 1–3 and filgrastim (Neupogen®; Amgen, Espoo, Finland) 5 μg/kg/day s.c. days 4–14. In the second, third and fourth courses, patients received the same drugs at standard doses: ifosfamide 3 g/m$^2$ i.v. day 1, 3–4 h infusion+mesna 50%, 25%, 25%, carboplatin 200 mg/m$^2$ i.v. day 1 and etoposide 120 mg/m$^2$ i.v. days 1–3. In courses 2, 3 and 4, filgrastim was always given if there was WHO grade 4 granulocytopenia ($<0.5 \times 10^9$/l) in two successive blood tests.

Patients, who had LD at diagnosis and who achieved a complete response (CR) or partial response (PR),

received radical doses of radiotherapy to the tumor area and mediastinum (2 Gy/day, 10 Gy/week up to the total dose of 50 Gy) 3 weeks after the induction chemotherapy, as did any extensive disease (ED) patients who achieved a complete response to the induction chemotherapy. The upper limit of treatment field was the fossa jugularis and the lower limit was the bifurcation of the trachea, to include the subcarinal lymph nodes, but excluding most of the heart. The maximum dose allowed to the medulla was 45 Gy. The doses were calculated to the ICRU point.

Responses were evaluated from computed tomography scans after the fourth course of induction treatment and after radiotherapy. Patients who had achieved no objective response to induction chemotherapy, or who had progressive disease, were excluded from the randomized part of study.

Tumor response was defined as follows: CR, complete disappearance of all known measurable and evaluable tumor from consecutive CT scans not less than 4 weeks apart; PR, 50% or greater decrease of tumor load, without the appearance of any new lesions or progression of any lesion; and progression (PD), an increase of more than 25% in one or more measurable or assessable lesions, or the appearance of a new lesion. All other evaluable circumstances were classified as stable disease (SD). Patients were evaluable for response after two courses of chemotherapy or after one course if there was disease progression.

Response duration was the time from the initial documented response to the first documented sign of progression. Survival was calculated from the first dose of chemotherapy until death. Time to progression was calculated from the first dose of chemotherapy to the first documented sign of progression.

Patients in whom CR or PR were observed at restaging, after the completion of chemotherapy, were randomly assigned to one of three maintenance groups. Those patients who had ED at diagnosis were randomly assigned at the first restaging after the induction chemotherapy. Those patients who had LD at diagnosis were randomly assigned at the second restaging after thoracic radiotherapy. The first maintenance therapy group received IFN-α and retinoid (Arm 1), the second group received trophosphamide chemotherapy (Arm 2), and the third group acted as the control group (Arm 3). Patients who achieved a CR or had minimal residual disease also received prophylactic cranial irradiation (PCI) 24 Gy (2 Gy/day 12 fractions).

In Arm 1, patients received IFN-α-2a (Finnferon®; SPR Veripalvelu, Helsinki, Finland/Roferon-A®; Roche, Espoo, Finland) as maintenance treatment 6 MIU s.c. TIW for 4 weeks, followed by 3 MIU s.c. TIW. Simultaneously with IFN treatment they received 13-*cis*-retinoic acid (Roaccutan®; Roche) 1 mg/kg/day p.o. BID daily from day 1. In Arm 2, patients received trophosphamide (Ixoten®; 50 mg/tablet; Asta Medica) 100–150 mg/day p.o. BID. Arm 3 was the control group (no maintenance treatment). All maintenance treatment was started 4–6 weeks after radiotherapy or 4–6 weeks after the fourth chemotherapy cycle. It was given for 12 months, but stopped earlier if progression or severe side effects were observed. In this case second-line topotecan or best supportive care was given.

The following procedures and measurements were carried out before the first course of induction treatment, before the beginning of maintenance treatment and when all active treatment was discontinued: chest X-ray, CT scan of thorax and upper abdomen, ECG; complete blood count, CRP, sodium, potassium, creatinine, creatinine clearance, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase, bilirubin, cholesterol, triglyceride, calcium, neuron-specific enolase (NSE), and ultrasound of the heart, if necessary.

Before each chemotherapy cycle and in days 10–14 of each cycle the following were required: complete blood count, CRP, and creatinine, sodium and potassium levels. Before each cycle a chest X-ray was taken and alkaline phosphatase levels were measured.

For the evaluation of therapeutic response, a clinical investigation as well as a CT scan of the chest and upper abdomen (plus bronchoscopy if necessary to confirm complete response) were performed before the start of both the induction and the maintenance treatments, and whenever a patient left the study for whatever reason. A brain CT scan was performed before PCI.

During maintenance treatment, chest X-rays were taken every second month, and CT scans of the chest and upper abdomen were performed every fourth month, at the end of maintenance treatment and as necessary. Patients underwent a complete blood count, CRP, and measurement of creatinine, ASAT, ALAT and bilirubin levels every 4 weeks. Cholesterol and triglyceride levels were also measured in Arm 1 patients every 4 weeks. Clinical investigations were performed at least every 2 months, and more frequently if necessary (Arm 3 patients included).

If neutrophil levels were $0.5–0.99 \times 10^9$/l or platelet levels were $50–74 \times 10^9$/l before a chemotherapy cycle, patients received 75% of the scheduled chemotherapy doses. If neutrophils were $< 0.5 \times 10^9$/l or platelets $< 50 \times 10^9$/l before a chemotherapy cycle, the chemotherapy was not administered. The levels were measured again after one week.

Patients were randomly allocated to Arm 1, Arm 2 or Arm 3 using block randomization.

All patients who received at least one dose of combination chemotherapy were evaluable for safety of the induction treatment. Patients who received at least one dose of maintenance therapy were evaluable for safety of the maintenance treatment. Toxicity was graded according to the WHO criteria. All patients who were enrolled in the study and met the eligibility criteria qualified for objective tumor response assessment and for analysis of the time-to-event parameters.

### Statistical analysis

Statistical analyses were performed using the BMDP (University of California, 1992) and StatXact 4 (Cytel Software Corporation 1995) software packages. Survival rates and curves were calculated using the Kaplan–Meier method. The log-rank (Mantel–Cox) test was used to compare the survival curves and analysis of variance was used to compare group means of the continuous variables. The differences were tested using the generalized Fisher's exact test for $R \times C$ contingency tables. All $p$ values reported are two-sided and $p<0.05$ was considered significant.

## Results

Between March 1995 and February 1999, 85 patients with histologically or cytological confirmed, without prior chemotherapy, stage I–IV SCLC were entered in the study.

After induction chemotherapy or after induction chemotherapy and radiotherapy, 60 patients in whom CR or PR was observed were randomly assigned for maintenance treatment. Seventeen patients were randomly allocated to the IFN–retinoid arm, 23 patients to the trophosphamide arm and 20 patients to the control arm. Twenty-five patients, who had achieved no objective response to induction chemotherapy or who had progressed, were excluded from the study and they continued with symptomatic treatment. Patient characteristics are described by treatment arm in Table 1.

The three arms of the study were well balanced with respect to age, sex and performance status. There were slightly more patients (55%) with LD than with ED.

The response rates to the induction therapy are given in Table 2 and were determined according to WHO criteria, as the best response from at least two consecutive courses of chemotherapy with a confirmatory tumor evaluation at least 1 month later. There was no statistically significant difference in

**Table 2.** Best response to chemotherapy + radiotherapy ($n$=85)

| | | IFN | Ixoten | Control | Not randomized |
|---|---|---|---|---|---|
| CR | 21 | 5 | 7 | 8 | 1 |
| MRD | 4 | 2 | 0 | 2 | 0 |
| PR | 42 | 10 | 16 | 10 | 6 |
| NC | 6 | 0 | 0 | 0 | 6 |
| NE | 11 | 0 | 0 | 0 | 11 |
| PD | 1 | 0 | 0 | 0 | 1 |

$p$=0.44.

**Table 1.** Patient characteristics

| | Total | IFN | Ixoten | Control | Not randomized |
|---|---|---|---|---|---|
| No. of patients | 85 | 17 | 23 | 20 | 25 |
| M/F | 58/27 | 11/6 | 16/7 | 12/8 | |
| Age (years) | | | | | |
| median | 61 | 58 | 60 | 57 | 60 |
| range | 39–74 | | | | |
| Karnofsky's performance status (%) | | | | | |
| 100/90 | 15/31 | 5/6 | 5/9 | 0/7 | 5/9 |
| 80 | 24 | 2 | 7 | 9 | 6 |
| <80 | 15 | 4 | 2 | 4 | 5 |
| median (%) | 90 | 90 | 90 | 90 | 90 |
| Stage | | | | | |
| I | 6 | 4 | 1 | 1 | 1 |
| II | 1 | 0 | 0 | 0 | 1 |
| IIIA | 9 | 0 | 7 | 2 | 0 |
| IIIB | 31 | 5 | 5 | 10 | 11 |
| IV | 37 | 9 | 10 | 7 | 11 (1 NE) |
| LD | 47 (55%) | 8 | 13 | 13 | 13 |
| ED | 37 (44%) | 9 | 10 | 7 | 11 (1 NE) |

response rate between the groups. Eleven patients were unevaluable for response: one had been wrongly diagnosed, five suffered an early death and five did not receive the full treatment [one patient violated protocol (too old), two did not receive any chemotherapy and two received only one course of chemotherapy].

Median duration of maintenance treatment was 4.2 months both in the IFN-α–retinoic acid arm and in the trophosphamide arm. Median survival for the patients in Arm 1 (IFN-α–retinoid) was 17.7 months, in Arm 2 (trophosphamide) 13.5 months and in Arm 3 (control) 16.2 months. The 1-year survival rates were 82% for Arm 1, 56% for Arm 2 and 55% for Arm 3. The disease-free interval was 6.5 months in Arm 1, and 5.5 and 4.7 months in Arms 2 and 3, respectively. Time to progression was 8.6 months in Arm 1, and 8.0 and 6.8 months in Arms 2 and 3, respectively. Time from PD to death was 7.8, 3.1 and 3.3 months, respectively. There were no statistically significant differences. The survival curves are shown in Figure 1.

Hematological toxicity during induction chemotherapy was graded according to WHO guidelines and is given in Table 3. The most common hematological toxicity was grade 3 (13%) and 4 (14%) leukopenia and thrombocytopenia. The most common non-hematological toxicity was allergic reaction to the mesna infusions (5% of patients). Three deaths occurred when using the initial four-drug regime consisting of epirubicin (a 63-year-old man with infection, a 65-year-old man with a myocardial infarction and lung oedema, and a 64-year-old woman with GI hemorrhage). The regime was modified to exclude epirubicin, because we could not exclude the possibility that the deaths were treatment related. During maintenance treatment there were only two grade 3 non-

**Table 3.** Toxicity of induction chemotherapy (*n*=85): no. of cycles in original four-drug protocol, 10; no. of cycles in modified three-drug protocol, 286

| | Grade 3 | Grade 4 |
|---|---|---|
| Hematological (no. of cycles) | | |
| Leukopenia | | |
| original protocol (+ epirubicin) | 1 | 4 (40%) |
| modified protocol (no epirubicin) | 38 (13%) | 39 (14%) |
| Thrombocytopenia | | |
| original protocol (+ epirubicin) | 2 | 3 (30%) |
| modified protocol (no epirubicin) | 16 (5%) | 21 (7%) |
| Anemia | 1 | |
| | | |
| Non-hematological (no. of cycles) | | |
| Grade 3 | | |
| liver enzymes increased | 2 | |
| angina pectoris | 1 | |
| Grade 1–2 | | |
| allergic reaction | 15 (5%) | |
| cystitis (ifosfamide) | 3 | |
| ifosfamide encephalopathia (?) | 1 | |
| atrial fibrillation | 2 | |
| myocardial infarction | 2 (original protocol) | |
| sepsis | 4 | |
| pulmonary abscess | 1 | |
| hypocalcemia | 5 | |
| hyponatremia | 1 | |
| sinus takycardia | | |

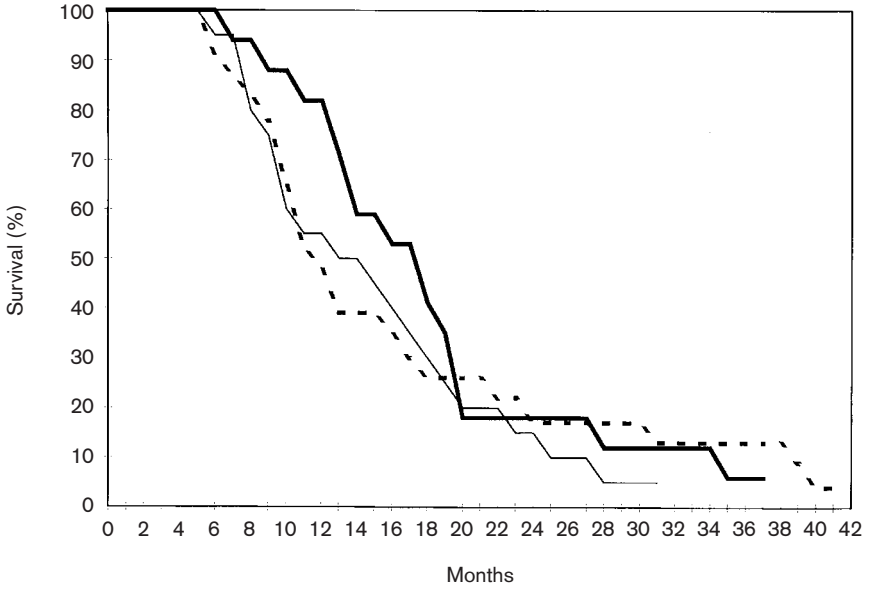


**Figure 1.** Survival of 65 patients with SCLC according to maintenance therapy. Heavy line, IFN-α+retinoic acid (*n*=17); broken line, trophosphamide (*n*=23); light line, control (*n*=20).

**Table 4.** Duration of maintenance treatment, duration of response, time to progression, time from PD to death, 1-year survival and median survival

| | IFN | Ixoten | Control | |
|---|---|---|---|---|
| Duration of maintenance treatment, median (months) | 4.2 | 4.2 | | |
| *N* | 17 | 23 | | |
| Duration of response, median (month) | 6.5 | 5.5 | 4.7 | $p=0.24$ |
| *N* | 12 | 18 | 16 | |
| Time to progression, median (months) | 8.6 | 8.0 | 6.8 | $p=0.31$ |
| *N* | 12 | 18 | 16 | |
| Time from PD to death, median (months) | 7.8 | 3.1 | 3.3 | $p=0.27$ |
| *N* | 10 | 18 | 13 | |
| One-year survival (no. of patients) | 14/17 | 13/23 | 11/20 | $p=0.18$ |
| % | 82 | 56 | 55 | |
| Survival, median (months) | 17.7 | 13.5 | 16.2 | $p=0.79$ |
| *N* | 17 | 23 | 20 | |

hematological toxicity events, one case of nausea in the IFN-α–retinoic acid arm and one case of grade 3 leukopenia in the trophosphamide arm. One episode each of grade 1 hypercholesterolemia and grade 1 hypertriglyseridemia also occurred during IFN–retinoid maintenance treatment.

Brain metastases were fewer in the IFN arm than in the trophosphamide or the control arms, but the difference was not statistically significant.

Duration of maintenance treatment, duration of response, time to progression, 1-year survival rates, median survival and time from PD to death are shown in Table 4.

## Discussion

SCLC responds initially to chemotherapy, but the remission is difficult to maintain. Various forms of maintenance chemotherapy have been studied. Sculier carried out a critical review of the literature on maintenance chemotherapy for SCLC. One study showed a statistically significant difference in survival in favor of maintenance treatment and five obtained some survival advantage in certain subgroups of patients. Another study reported a significantly shorter survival for patients receiving maintenance treatment and in six studies there was no difference in survival between the arms.[13] A quantitative overview or meta-analysis was impracticable, because of the lack of data for calculating the odds ratio from the publications and because of the heterogeneity of study design. Sculier concluded that maintenance CT could have some indications and that further good quality trials need to be carried out. Trillet-Lenoir's group has made a meta-analysis of this topic, based on the published data from 15 randomized trials. They also concluded that further well-designed randomized clinical trials of maintenance chemotherapy for SCLC are needed.[14]

It is therefore of interest to seek novel treatments to maintain remission in SCLC. Biological response modifiers with anti-neoplastic activity, like IFN, have stimulated investigators to design studies using this agent to maintain response in SCLC. IFN-α's anticancer activity is based on variety of properties, which involve both direct and indirect action on tumor cells. Direct anti-tumor actions include anti-proliferative effects, cytotoxic effects and enhancement of antigen expression on the cell surfaces of tumor cells. Indirect actions include activation of macrophages/monocytes, activation of T cells, activation of NK cells and modulation of antibody production.[15] IFNs have anti-angiogenetic properties, they are known to inhibit vascular proliferation.[16] Since the 1970s, when Cantell and the Finnish Blood Bank was able to produce sufficient quantities of crude IFN-α from buffy coat layers for clinical use, several trials have been performed in lung cancer, first using natural IFN-α and later using different combinations of recombinant IFN. Very high-dose or low-dose natural IFN-α monotherapy did not induce objective responses in SCLC, nevertheless it stabilized the disease for a significant duration of time to indicate that IFN-α has biological activity against SCLC. In most studies in SCLC, both natural and recombinant IFN-α were given concurrently with chemotherapy or used as maintenance treatment after induction chemotherapy. A great variety of study design and dosage schedules were used in the earlier IFN maintenance studies, and some problems were encountered. In Kelly's study, using a rather high dosage of recombinant IFN-α, only a few patients could complete the IFN-α maintenance treatment protocol because of intolerable side-effects.[17] In Tummarello's study, despite encouraging results, the number of patients was too small to evaluate the role of IFN-α in maintenance treatment (only 14 patients in IFN-α arm).[18] Mattson, on the other hand, achieved a clear difference in long-term survival in a large randomized study of IFN-α maintenance therapy following induction chemo- and radiotherapy for patients with SCLC, using low-dose natural-IFN-α.[7] In another phase III study, Prior also showed that the IFN maintenance arm patients survived longer than those in the chemotherapy arm ($p<0.02$).[19] In a study evaluating concomitant chemotherapy and IFN-α for SCLC, we showed that low-

dose IFN-α can be administered concomitantly with standard chemotherapy, but that optimal full doses of chemotherapy could not be given because of hematological toxicity.[8] In Lebeau's study, patients were treated with six courses of chemotherapy ± thoracic radiotherapy and PCI, and then the patients were randomly assigned to control (no maintenance treatment) or IFN-α maintenance treatment. The estimated 2-year survival rates were 22% in the IFN-α group and 13% in the control group; the estimated complete response rates at 2 years were 22 and 15%, respectively.[20] Results are thus conflicting.

Preclinical data indicate that the combination of retinoids and IFN have synergistic anti-proliferative and differentiating effects in some hematological and solid tumor models.[21] Two trials using a combination of IFN and retinoids in patients with non-small cell lung cancer (NSCLC) have been completed. In the first,[22] only patients with squamous histology were eligible and prior chemotherapy was permitted. Only one response of brief duration was observed in 17 patients. In the second trial,[23] the patients had not received prior chemotherapy. One response was seen in the 17 patients in the squamous histology cohort and none in the 17 patients with non-squamous histologies. A possible mechanism of action of this combination could be that retinoids increase the expression of interferon receptors, thus rendering tumor cells more susceptible to the anti-proliferative effects of IFNs. Another possible explanation for the enhanced anti-tumor effect of this combination of agents could be their inhibitory effects on tumor angiogenesis.

All these earlier results provided the rationale for the present study, where adequate induction chemotherapy was followed by an intensified combined biological maintenance treatment consisting of IFN-α and retinoid acid.

This is the first study of IFN-α and retinoid acid in SCLC. We have been able to show that it is feasible to administer a combination of retinoids and IFN-α for 12 months as maintenance therapy after high-dose chemotherapy and radiotherapy, without any grade 3–4 toxicities. The study was designed as a randomized phase II feasibility study, so that patients were randomized before maintenance therapy in order to test the design for a potential future phase III study. We ran two control arms, no treatment maintenance or maintenance treatment using a low-dose single-agent oral chemotherapy. Median survival of 13.5–17.7 months and a 1-year survival rate of 55–82% indicated that the induction chemo-radiotherapy was adequate. Median duration of IFN-α and retinoid acid maintenance treatment was 4.2 months. The main cause for treatment discontinuation was disease progression. Median time to progression and median duration of response were not significantly better in the IFN-α–retinoid arm, but there was a trend towards better 1-year survival figures in the IFN-α–retinoid arm. The patients in the IFN-α–retinoid arm also tended to live longer after the development of progressive disease, but the difference was not statistically significant.

The continuing improvement in the understanding of the biochemical pathways that lead to tumor growth has focused on new targets for anti-neoplastic agents. Recently novel anticancer agents have emerged for clinical use, such as signal transduction inhibitors and angiogenesis inhibitors. Inhibition of angiogenesis provides a promising new strategy for cancer therapy and would be of particular value as an adjuvant treatment after primary ablative therapy.[24] The inhibitory effect of IFNs on the process of angiogenesis was already known in the 1980s.[16] The combination of IFNs with new anti-angiogenesis agents could potentiate anti-angiogenetic activity. To optimize maintenance therapy in SCLC using biological agents, we recommend further studies of IFN and some of the new anti-angiogenetic factors.

## Acknowledgments

We thank Mrs Anne Hand for language revision and editorial advice.

## References

1. Österlind K, Spiro SG, ed. Carcinoma of the lung. Chemotherapy in small-cell lung cancer. *Eur Resp Monogr* 1995; **1** (monogr 1): 306–31.
2. Dorward A, Banham S, Hutcheon A, *et al*. Short duration combination chemotherapy in the treatment of small cell lung cancer. *Thorax* 1986; **41**: 688–91.
3. Elias A. Dose intensive combined modality therapy for small cell lung cancer. *Lung Cancer* 1994; **11** (suppl): 136–37.
4. Klasa RJ, Marray N, Coldman AJ. Dose-intensity meta-analysis of chemotherapy regimes in small-cell carcinoma of the lung. *J Clin Oncol* 1991; **9**: 499–508.
5. Chute JP, Chen T, Feigal E, *et al*. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. *J Clin Oncol* 1999; **17**: 1794–801.
6. Mattson K, Holsti LR, Niiranen A, *et al*. Human leukocyte interferon as part of a combined treatment for previous untreated small cell lung cancer. *J Biol Resp Modif* 1985; **4**: 8–17.
7. Mattson K, Niiranen A, Pyrhönen S, *et al*. Natural interferon alfa as maintenance therapy for small cell lung cancer. *Eur J Cancer* 1992; **28A**: 1387–91.

8. Ruotsalainen TM, Halme M, Tamminen K, *et al*. Concomitant chemotherapy and IFN-α for small cell lung cancer: a randomized multicenter phase III study. *J Interferon Cytokine Res* 1999; **19**: 2539.
9. Mattson K, Niiranen A, Ruotsalainen T, *et al*. Interferon maintenance therapy for small cell lung cancer: Improvement in long-term survival. *J Interferon Cytokine Res* 1997; **17**: 103–5.
10. Bollag W, Holdener E. Retinoids in cancer prevention and therapy. *Ann Oncol* 1992; **3**: 513–26.
11. Bollag W, Malewski S, Jablonska S. Cancer combination chemotherapy with retinoids: experimental rationale. *Leukemia* 1994; **8** (suppl 3): S11–5.
12. Toma S, Palumbo R, Vincenti M, *et al*. Efficacy of recombinant alpha-interferon 2a and 13-*cis*-retinoic acid in the treatment of squamous cell carcinoma. *Ann Oncol* 1994; **5**: 463–5.
13. Sculier JP, Berghmans T, Castaigne C, *et al*. Maintenance chemotherapy for small cell lung cancer: a critical review of the literature. *Lung Cancer* 1998; **19**: 14151.
14. Trillet-Lenoir V, Cucherat M, Gérard JP, *et al*. Maintenance chemotherapy for small cell lung cancer. *Lung Cancer* 1998; **21**: 221–3.
15. Fleischmann WR, Fleischmann CM. Mechanisms of interferons' antitumour actions. In: Baron S, Copperhaver DH, Dianzani F, *et al*., eds. *Interferon: principles and medical applications*, 1st edn. Galveston, TX: University of Texas Medical Branch 1992: 299–309.
16. Sidky YA, Borden EC. Inhibition of angiogenesis by interferons. *Cancer Res* 1987; **47**: 5155–61.
17. Kelly K, Crowley JJ, Bunn PA Jr, *et al*. Role of recombinant interferon alfa-2a maintenance in patients with limited-stage small-cell lung cancer responding to concurrent chemoradiation: a Southwest Oncology Group study. *J Clin Oncol* 1995; **13**: 2924–30.
18. Tummarello D, Mari D, Graziano F, *et al*. A randomized, controlled phase III study of cyclophosphamide, doxorubicin, and vincristine with etoposide (CAV-E) or teniposide (CAV-T), followed by recombinant interferon-alpha maintenance therapy or observation, in small cell lung carcinoma patients with complete responses. *Cancer* 1997; **80**: 2222–9.
19. Prior C, Oroszy S, Oberaigner W, *et al*. Adjunctive interferon-α-2c in stage IIIB/IV small cell lung cancer: a phase III trial. *Eur Resp J* 1997; **10**: 392–6.
20. Lebeau B, De La Salmoniere P, Ozenne G, *et al*. *Proc Am Soc Clin Oncol* 1999; **18**: 475a (abstract 1832).
21. Eisenhauer EA, Lippman SM, Kavangh JJ, *et al*. Combination of 13-*cis*-retinoic acid and interferon-alpha-2a in the therapy of solid tumors. *Leukemia* 1994; **8**: 1622–5.
22. Rinaldi DA, Lippman SM, Burris HA, *et al*. Phase II study of 13-*cis*-retinoic acid and interferon-alpha-2a in patients with advanced squamous cell lung cancer. *Anti-Cancer Drugs* 1993; **4**: 33–6.
23. Arnold A, Ayoub J, Douglas L, *et al*. Phase II trial of 13-*cis*-retinoic acid and interferon-alpha in non-small cell lung cancer. *J Natl Cancer Inst* 1994; **86**: 306–9.
24. Sausville EA. New agents—noncytotoxins, antiangiogenesis. In: Perry MC, ed. *Fall educational book ASCO*. Chicago, IL: ASCO 1998: 112–7.

*(Received 28 October 1999; revised form accepted 11 November 1999)*